Received: 22 November 2021 | Accepted: 7 February 2022

DOI: 10.1002/hep4.1926

ORIGINAL ARTICLE

A pilot study of vidofludimus calcium for treatment of primary sclerosing cholangitis

Elizabeth J. Carey[1] | **John Eaton**[2] | **Mitchell Clayton**[2] | **Andrea Gossard**[2] | **Sara Iqbal**[3] | **Hamid Ullah**[3] | **Nan Zhang**[4] | **Richard Butterfield**[4] | **Keith D. Lindor**[1]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Phoenix, Arizona, USA

[2]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA

[3]Gastroenterology, West Virginia University, Morgantown, West Virginia, USA

[4]Department of Quantitative Health Research, Mayo Clinic, Phoenix, Arizona, USA

Correspondence
Elizabeth Carey, Division of Gastroenterology & Hepatology, Mayo Clinic in Arizona, 5779 E. Mayo Blvd, Phoenix, AZ 85050, USA.
Email: carey.elizabeth@mayo.edu

Funding information
Supported by Immunic Therapeutics, Munich, Germany, and a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (R21DK118358-03 to X.X.)

Abstract

The purpose of this pilot study was to explore the efficacy, safety, and tolerability of vidofludimus calcium (VC) in the treatment of primary sclerosing cholangitis (PSC). This was a single-arm open-label pilot study with a cohort of 18 patients with PSC. Study patients received VC for a period of 6 months. The study was undertaken at two sites, Mayo Clinic, Rochester, MN, and Mayo Clinic, Phoenix, AZ. The primary endpoint of the study was improvement of serum alkaline phosphatase (ALP) at the end of the study. Secondary endpoints included assessment of other liver biomarkers (bilirubin, alanine aminotransferase, and aspartate aminotransferase). Of 18 patients enrolled, 11 completed the 6 months of study treatment. Patients who completed treatment versus those who did not were similar other than a significantly higher direct bilirubin at baseline in the group that completed treatment (mean ± SD, 0.4 ± 0.3 versus 0.1 ± 0.1, p = 0.04). By intent to treat analysis, the primary outcome was met in 16.7% (3/18) of patients. By per-protocol analysis, including only patients who completed treatment, normalization of ALP occurred in 27.7% (3/11) at week 24 (95% confidence interval, 6.0% to 61.0%). VC was well tolerated with no drug-related serious adverse events. *Conclusion:* This proof of concept study provides support for further exploration of VC in patients with PSC.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is an idiopathic, chronic, cholestatic liver disease that is distinguished by inflammation and fibrosis of the bile ducts, resulting in end-stage liver disease and reduced life expectancy. The prevalence of PSC in the United States is roughly 1–16 individuals per 100,000.[1] It is most common in young and middle-aged men but in the absence of inflammatory bowel disease (IBD) tends to favor the female sex.[2] The etiology of PSC is speculated to be an amalgamation of immune-mediated components, genetic predilection,[3] and their interaction with the biome.[4]

The presentation of PSC constitutes a cholestatic pattern of liver injury with predominant elevation of alkaline phosphatase (ALP).[1] ALP elevation is a strong predictor of prognosis and is currently considered

the best surrogate endpoint for clinical research.[5,6] Normalization of serum ALP appears to be associated with long-term survival free of cholangiocarcinoma, liver transplantation, liver-related death, and colorectal cancer, while persistent ALP elevation has been associated with worse outcomes in PSC.[7]

The lack of pharmacologic therapy for this devastating disease makes it a topic of intense clinical investigation. The presence of IBD in 85% of patients with PSC[2] suggests a shared proinflammatory cytokine association between the two diseases. A central role of interleukin 17 (IL-17) in the pathogenesis of PSC is noted.[8,9] Vidofludimus calcium (VC) is a new dihydroorotate dehydrogenase inhibitor (DHODH) that catalyzes the rate-limiting step in the pyrimidine synthesis pathway and induces apoptosis in proliferating lymphocytes. It also leads to reduction in the release of the proinflammatory cytokines IL-17 and interferon gamma. VC is also a partial farnesoid X receptor (FXR) agonist; by decreasing fibrosis and regulating bile acid homeostasis, FXR agonists are currently among the most promising novel treatment developments for cholestatic liver disease. VC has shown promising results in a recent trial performed on patients with ulcerative colitis,[10] and a series of clinical trials has demonstrated a highly favorable safety profile.[11–14] In this pilot proof of concept study, we sought to determine the effect of VC on PSC.

PARTICIPANTS AND METHODS

Patients

Potential subjects were adults (ages 18–75 years) with a diagnosis of PSC consistent with American Association for the Study of Liver Diseases published guidelines. All subjects were required to have an elevated serum alkaline phosphatase (ALP) of at least 1.5 times the upper limit of normal (ULN) and an indirect bilirubin within 1.2 times the ULN at screening. Patients with or without concomitant IBD were eligible to participate.

Potential subjects were excluded from the study if they met any of the following exclusion criteria: pregnancy or anticipated pregnancy; active hepatitis A, B, or C infection; other cholestatic liver diseases; immunoglobulin G4-related cholangitis; human immunodeficiency virus (HIV)/acquired immune deficiency syndrome; tuberculosis; serum uric acid levels >1.2 times the ULN at screening; PSC with autoimmune hepatitis overlap; secondary sclerosing cholangitis; cholangiocarcinoma; a previous liver biopsy showing nonalcoholic steatohepatitis; presence of complications of advanced PSC, such as hepatic encephalopathy, portal hypertension, hepatorenal syndrome, or hepatopulmonary syndrome; history of or anticipated need for liver transplantation within 12 months of enrollment; Model for End-stage Liver Disease score ≥15; Child-Pugh score >6; a calculated creatinine clearance of <60 mL/minute; ongoing alcohol abuse; evidence of or treatment for *Clostridioides difficile* or other intestinal pathogens within 30 days of initiating the study drug; use of methotrexate at a dose of ≥17.5 mg/week or use of rosuvastatin exceeding 10 mg daily; any other conditions or abnormalities that, in the opinion of the Principal Investigator, could compromise subject safety or study validity.

Study medication

Participants received VC 30 mg (Immunic AG, Munich, Germany) by mouth once daily after a 1-week lead-in dose period where they received VC 15 mg by mouth once daily.

Study design

This investigator-initiated, open-label, single-armed clinical trial was conducted at the Mayo Clinic in Phoenix, AZ, and Rochester, MN, after being approved by Mayo Clinic's Institutional Review Board. Informed consent was obtained from each patient in writing, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Potential subjects completed screening and baseline visits within 1 month of initiating the study drug. Visits included obtaining informed consent, reviewing medical history and current medications, a physical exam and vital signs, and laboratory assessments (ALP, AST, ALT, total and direct/indirect bilirubin, uric acid, HIV, tuberculosis, creatinine with estimated glomerular filtration rates [if not available in the medical record], viral hepatitis testing [if not available in the medical record], and urine pregnancy testing [for women of child-bearing potential]).

After the screening visit, inclusion and exclusion criteria were assessed by the enrolling site's Principal Investigator, and the subject was shipped study medication if eligible. Subjects completed a 1-week lead-in dose period where they received VC 15 mg once daily. If well-tolerated, subjects received VC 30 mg once daily until the end of the treatment phase at week 24. During the first 2 weeks of the treatment phase, subjects self-administered for hematuria testing by urine dipstick every other day.

Subjects were called by telephone at weeks 2, 4, 8, 12, 16, and 20 during the treatment period and at week 28 during the follow-up period. Current medications, adverse events (AEs), PSC- and IBD-related complications, and adherence to the protocol were evaluated. Subjects also had a local blood draw at these time points, and testing for ALP, AST, ALT, and total and direct/indirect bilirubin were completed. At the end of

the 6-month treatment phase, subjects returned to the clinic for their final visit before entering the 4-week follow-up period.

Study endpoints

The primary endpoint was an improvement in serum ALP at months 3 and 6 compared to baseline. A 25% improvement in ALP with no more than a 33% worsening of AST after 6 months of treatment was assessed as a positive outcome, indicating that VC may have a positive effect on the progression of PSC. Secondary endpoints included improvement of total and direct bilirubin, AST, and ALT at months 3 and 6 versus baseline.

Statistical analysis

Demographics and clinical characteristics were compared between those patients who had completed treatment and those who had not. The proportion of patients to reach the primary endpoint at 6 months and their corresponding confidence intervals (CIs) was estimated using the exact binomial method. Success was defined as a 95% CI that did not overlap 0 at 6 months.

To quantify the overall time trend for liver chemistries, a mixed model using random intercept (to take within-patient correlation into account) was used. Time from baseline was calculated as a continuous variable and treated as the primary predictor in the model. Each laboratory value at the time of acquisition was treated as the outcome. To better quantify the time effect, every 30-day increase was used for the time. Age at baseline and sex were also adjusted in the model.

The incidence, type, and relatedness of serious AEs and AEs were monitored and reported for all subjects.

RESULTS

Enrollment began on July 1, 2019, and closed in September 2020. A total of 18 patients were accrued into the study, 11 of whom completed treatment. A detailed summary of the patient accrual is provided in Table 1.

Baseline characteristics were comparable between the two groups (Table 2). The majority were women at the time of accrual, comprising 61.1% of the total patient cohort. Of subjects who completed the treatment, 55.5% were women. All patients were Caucasian. Over half (54.5%) of patients had a concomitant diagnosis of IBD. Only 9% had a family history of PSC. Patients who completed treatment had significantly higher direct bilirubin at baseline compared to patients who did not complete treatment (mean [SD], 0.4 [0.3] vs. 0.1 [0.1], p = 0.039); there was no difference in total bilirubin. The number of subjects who had a history of colectomy, colonic malignancy or dysplasia, or history of IBD was similar in both groups. No patient had cirrhosis.

TABLE 1 Patient accrual

Total Accrual Patient Status	n = 18
Treatment complete	11 (61.1%)
Treatment incomplete	7 (38.9%)
Incomplete treatment	n = 7
Patient refusal/withdrawal of consent	3 (42.9%)
Toxicity/adverse event*	2 (28.6%)
Investigator's decision	1 (14.3%)
Lost to follow-up	1 (14.3%)
Incomplete treatment patients; timing	n = 7
After leading dose week 1	1 (14.3%)
After week 2	1 (14.3%)
After week 4	1 (14.3%)
After week 8	1 (14.3%)
After week 12	1 (14.3%)
After week 16	1 (14.3%)
After week 20	1 (14.3%)

*One patient had hematuria during the lead-in dosing week; another patient had worsening liver enzymes attributed to cholangitis.

Primary outcome analysis

The primary outcome was at least a 25% reduction in ALP from baseline to week 24, with no greater than 33% rise in AST. One patient who completed the treatment was not able to get laboratories performed at week 24 due to corona virus disease 2019 (COVID-19) pandemic-related closures. For this patient, the week 20 laboratories were carried forward; a positive response was noted for both at weeks 20 and 28.

Per the intention-to-treat (ITT) analysis, 3 of the 18 (16.7%) patients reached the primary endpoint at week 24 (95% CI, 3.6%–41.4%). Per-protocol analysis, which included only patients who completed treatment (n = 11), showed that 3 (27.7%) patients reached the primary endpoint (95% CI, 6.0%–61.0%) (Table 3).

ALP remained elevated for all patients throughout the study. Two patients had an ALP < 1.5 × ULN at 12 weeks and 1 patient at 24 weeks.

Secondary outcome analysis

Serum biochemistries were recorded at baseline and week 24. AST and ALT at baseline were predictive of the week 24 value, e.g., if the AST/ALT was normal at baseline, it remained normal at week 24. Abnormalities in bilirubin at baseline also did not change at week 24; however,

TABLE 2 Demographics and baseline characteristics by treatment completeness

	Completeness of Treatment			
	Treatment Complete (n = 11)	Treatment Incomplete (n = 7)	Total (n = 18)	p Value
Age at enrollment, years				
Mean (SD), range	48.1 (16.7), 26–70	41.9 (12.9), 30–60	45.7 (15.2), 26–70	0.415*
Male sex (assigned at birth), n (%)				
Male	5 (45.5%)	2 (28.6%)	7 (38.9%)	0.637†
Race, n (%)				
White	11 (100.0%)	7 (100.0%)	18 (100.0%)	
Ethnicity, n (%)				
Not Hispanic or Latino	11 (100.0%)	6 (85.7%)	17 (94.4%)	0.389†
Hispanic or Latino	0 (0.0%)	1 (14.3%)	1 (5.6%)	
History of IBD, n (%)				
Yes	6 (54.5%)	6 (85.7%)	12 (66.7%)	0.316†
History of colectomy, n (%)				
Yes	3 (27.3%)	3 (42.9%)	6 (33.3%)	0.627†
ALP at baseline, IU/L				
Mean (SD), range	386.2 (147.3), 219–661	334.6 (100.4), 215–488	366.1 (130.4), 215–661	0.415*
AST at baseline, IU/L				
Mean (SD), range	79.4 (27.6), 33–118	77.1 (44.1), 39–173	78.5 (33.7), 33–173	0.319*
ALT at baseline, IU/L				
Mean (SD), range	103.4 (39.3), 28–142	107.0 (65.1), 48–196	104.8 (49.1), 28–196	0.856*
Total bilirubin at baseline, mg/dL				
Mean (SD), range	0.9 (0.5), 0.3–2.1	0.6 (0.2), 0.3–1.0	0.8 (0.5), 0.3–2.1	0.201*
Direct bilirubin at baseline, mg/dL				
Mean (SD), range	0.4 (0.3), 0–1.0	0.1 (0.1), 0–0.3	0.3 (0.3), 0–1.0	0.039*

*Wilcoxon rank-sum p value.
†Fisher's exact test p value.

TABLE 3 Primary outcome analysis

	Primary Outcome Achieved n/Total N (%)	95% CI
ITT	3/18 (16.7%)	3.6%, 41.4%
Per protocol	3/11 (27.3%)	6.0%, 61.0%

a downward trend was noted. Significant changes were not seen in the secondary outcomes analysis.

Longitudinal data analysis

Longitudinal values for ALP and total bilirubin are shown in Figures 1–4. The mixed model results for the ITT analysis are summarized in Table 4 and the per-protocol analysis in Table 5. Total bilirubin did not significantly change in the ITT or per-protocol analysis. In the per-protocol analysis, the ALP had a significant reduction over time (p = 0.041); however, a decrease was not noted in the ITT analysis (p = 0.578). There were no significant differences in other laboratory results.

Adverse events

A total of 36 AEs were reported in the study from 12 patients. The majority of AEs were grade 1 (n = 33), and only three AEs were grade 2. Four (11.1%) AEs were possibly, probably, or definitely attributed to the study drug. Hematuria was reported in 2 participants, one case of which was thought to be secondary to the study drug. The other patient had been followed for 2 years after cessation of the study drug with persistent hematuria. The most frequent AE was pruritus, which was not attributed to the study drug. A summary of all AEs is provided in Table 6. One miscarriage was reported at approximately week 3 of pregnancy. This AE was reviewed in detail by the Data Safety and Monitoring Board, which supported continuing the study without a significant change to the protocol.

DISCUSSION

In this first clinical trial using VC for the treatment of PSC, promising trends in ALP improvement were noted

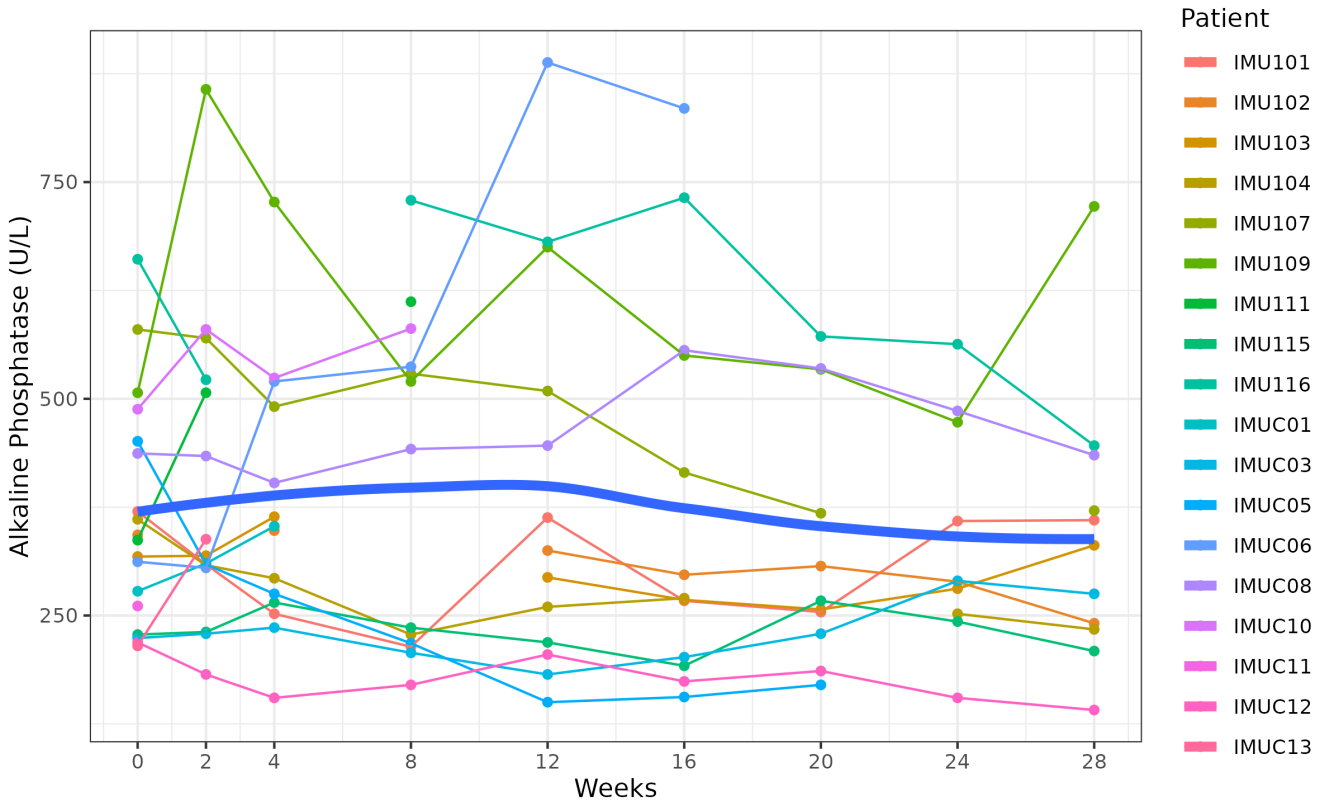

FIGURE 1 Longitudinal data analysis. ALP trend for the ITT analysis by time points

over 6 months of therapy. By per-protocol analysis, 27% of patients met the primary endpoint of ALP reduction by >25% with a no greater than 33% increase in AST. These data support further investigation into the potential of VC as a treatment for PSC.

VC combines the following two promising approaches in treating PSC: DHODH inhibition with a prominent influence on T-helper 17 (TH17)-induced inflammatory processes and farnesoid X receptor (FXR) agonism resulting in improved bile acid homeostasis and reduced fibrosis. As such, it is an ideal agent for PSC. It is a once-daily well-tolerated oral medication with promising results for multiple inflammatory diseases, including rheumatoid arthritis,[12] relapsing-remitting multiple sclerosis,[13] ulcerative colitis,[10] and coronovirus.[14]

Secondary endpoints were not met. Bilirubin, AST, and ALT did not significantly change over the course of the study. The safety profile was noted to be excellent. No severe AEs were reported. Of the AEs reported, only four were felt to possibly be related to the study drug (rise in ALP, rise in AST/ALT, hematuria, and fever). Of the 7 patients who did not complete the trial, 4 withdrew for reasons related to the pandemic (e.g., unwillingness to travel or have medical appointment exposure), 1 due to an episode of cholangitis, 1 for abdominal pain, and 1 for a rise in liver function tests that did not resolve after cessation of the study drug.

Some factors may have negatively impacted the results of this trial. First, the dose of VC in this study, 30 mg, was intentionally cautious and may have been too low to see a meaningful signal in a small trial. Doses of up to 40 mg have been successfully used in patients with IBD,[10] and 50 mg have been used in healthy adults.[11] The excellent safety profile noted in this pilot study adds strength to consider higher doses in future trials.

Second, the severe acute respiratory syndrome corona virus 2 (SARS CoV-2) pandemic affected multiple aspects of this trial. Almost all patients in the study were enrolled before pandemic-imposed travel restrictions, and the study was closed early when it became clear that new patient enrollment was futile in the setting of ongoing travel restrictions. Some patients had difficulty obtaining laboratories at the appropriate intervals, and 1 patient was unable to get blood drawn at week 20. Visits were converted to virtual/video visits when necessary to prevent the need for travel. The pandemic was cited as the reason for early withdrawal in 4 of 7 patients who did not complete the study.

There are several limitations to these results and the conclusions that can be drawn from this study. The number of patients enrolled was small, and the study suffered from a significant dropout rate. External factors, namely the SARS CoV-2 pandemic, accounted for most of the enrollment challenges rather than factors

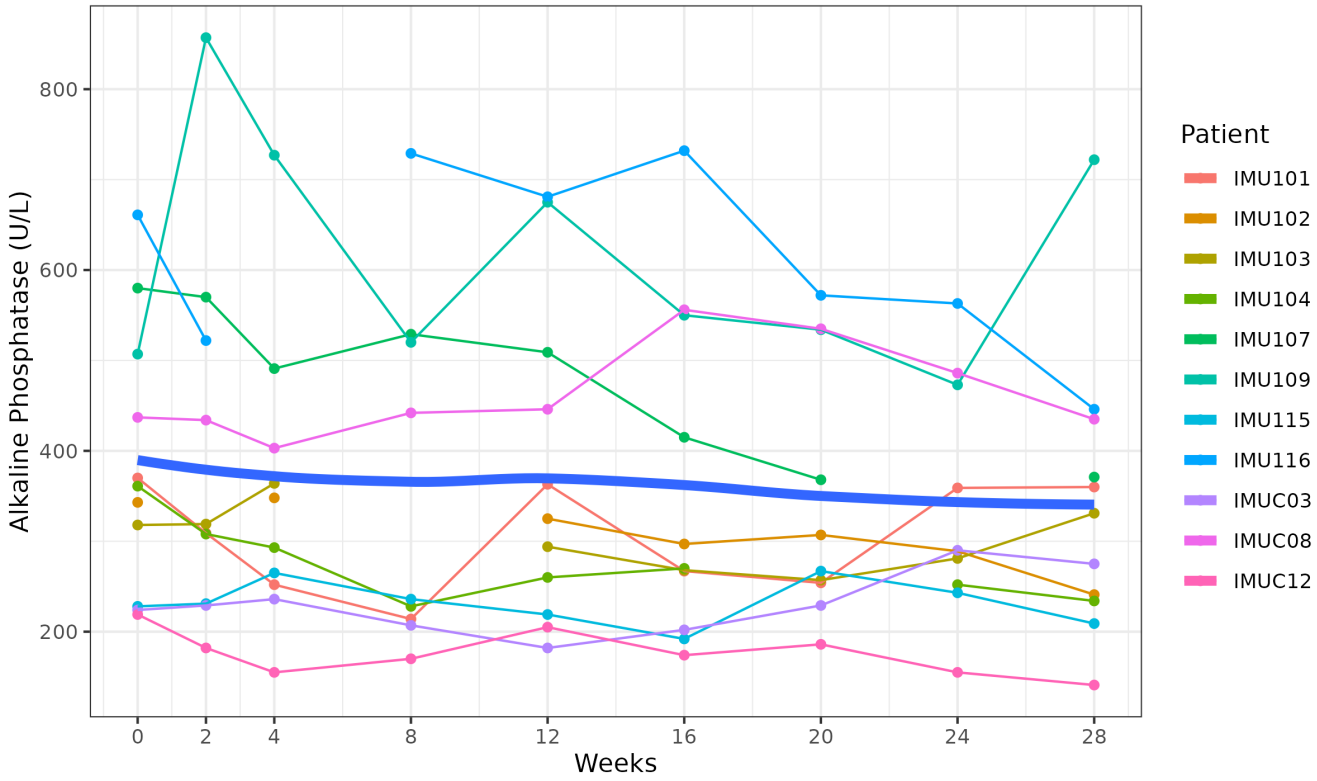

FIGURE 2 Longitudinal data analysis. ALP trend per-protocol analysis by time points

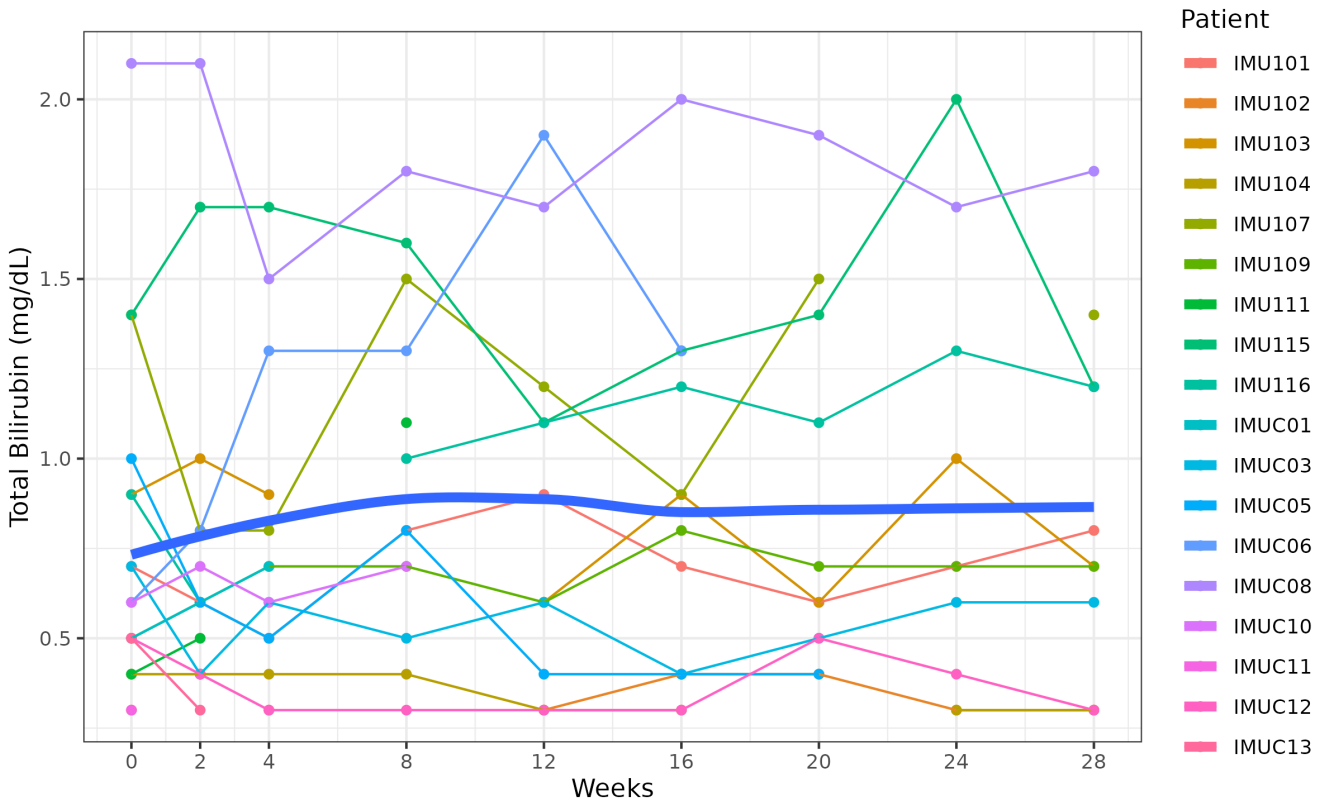

FIGURE 3 Longitudinal data analysis. Bilirubin trend for the ITT analysis by time points

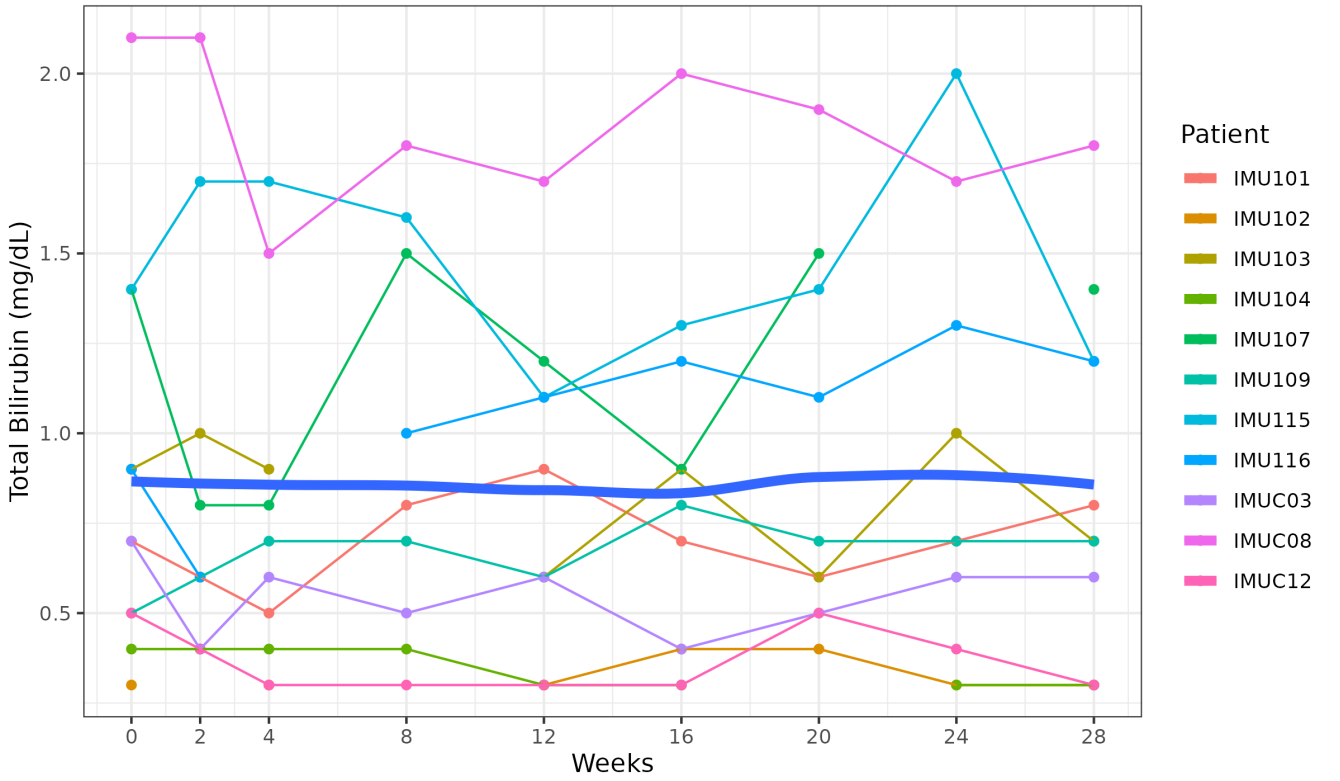

FIGURE 4 Longitudinal data analysis. Bilirubin trend per-protocol analysis by time points

TABLE 4 Longitudinal analysis of liver biochemistries, ITT (n = 18)

Outcome	Effect	Estimate (95% CI)	p value
ALP	Time from baseline (every 30-day increase)	–2.11 (–9.62, 5.40)	0.578
AST	Time from baseline (every 30-day increase)	1.24 (–0.99, 3.47)	0.272
ALT	Time from baseline (every 30-day increase)	0.93 (–2.37, 4.22)	0.578
Total bilirubin	Time from baseline (every 30-day increase)	0.01 (–0.01, 0.02)	0.345
Direct bilirubin	Time from baseline (every 30-day increase)	0.00 (–0.01, 0.01)	0.430

*All the models were adjusted for age at baseline and sex.

TABLE 5 Longitudinal analysis of liver biochemistries, per protocol (n = 11)

Outcome	Effect	Estimate (95% CI)	p value
ALP	Time from baseline (every 30-day increase)	–5.76 (–11.29, –0.23)	0.041
AST	Time from baseline (every 30-day increase)	1.22 (–0.53, 2.97)	0.170
ALT	Time from baseline (every 30-day increase)	0.85 (–1.46, 3.15)	0.467
Total bilirubin	Time from baseline (every 30-day increase)	0.00 (–0.01, 0.02)	0.561
Direct bilirubin	Time from baseline (every 30-day increase)	–0.00 (–0.01, 0.01)	0.861

*All the models were adjusted for age at baseline and sex.

intrinsic to the study itself. Nevertheless, it must be acknowledged that the conclusions in this study are based on a small number of patients. As a pilot study, it was an open-label trial without a placebo arm or randomization. In addition to the small study group, the population was comprised entirely of Caucasian patients, of whom the majority were women (characteristics that do not necessarily match the demographics of patients with PSC in general). All these factors limit the conclusions that can be drawn.

TABLE 6 Adverse event by attribution

Adverse Event	Attribution to Study Drug		Total (n = 36), n (%)
	Unrelated or Unlikely Related (n = 32), n (%)	Possible, Probable, and Definitely Related (n = 4), n (%)	
Abdominal pain	1 (3.1%)	0 (0.0%)	1 (2.8%)
ALP increased	0 (0.0%)	1 (25.0%)	1 (2.8%)
Allergic reaction	2 (6.3%)	0 (0.0%)	2 (5.6%)
Diarrhea	3 (9.4%)	0 (0.0%)	3 (8.3%)
Fatigue	1 (3.1%)	0 (0.0%)	1 (2.8%)
Fever pyrexia	1 (3.1%)	1 (25.0%)	2 (5.6%)
Headache	1 (3.1%)	0 (0.0%)	1 (2.8%)
Hematuria	1 (3.1%)	1 (25.0%)	2 (5.6%)
Nasal congestion	1 (3.1%)	0 (0.0%)	1 (2.8%)
Nausea	3 (9.4%)	0 (0.0%)	3 (8.3%)
Pruritus	4 (12.5%)	0 (0.0%)	4 (11.1%)
Stomach pain	1 (3.1%)	0 (0.0%)	1 (2.8%)
Urinary tract infection	1 (3.1%)	0 (0.0%)	1 (2.8%)
Achy neck and shoulders	1 (3.1%)	0 (0.0%)	1 (2.8%)
Bleeding from ileostomy	1 (3.1%)	0 (0.0%)	1 (2.8%)
Cold	2 (6.3%)	0 (0.0%)	2 (5.6%)
Discolored stool	1 (3.1%)	0 (0.0%)	1 (2.8%)
Flu	1 (3.1%)	0 (0.0%)	1 (2.8%)
Gastroenteritis	1 (3.1%)	0 (0.0%)	1 (2.8%)
Lipoma on back	1 (3.1%)	0 (0.0%)	1 (2.8%)
Miscarriage	1 (3.1%)	0 (0.0%)	1 (2.8%)
Upper right abdominal pain	1 (3.1%)	0 (0.0%)	1 (2.8%)
Worsened loose stools	1 (3.1%)	0 (0.0%)	1 (2.8%)
Worsening liver enzymes	0 (0.0%)	1 (25.0%)	1 (2.8%)
Cholangitis	1 (3.1%)	0 (0.0%)	1 (2.8%)

The choice of endpoints in clinical trials for PSC is an ongoing challenge. For this small pilot study, change in ALP was chosen as the primary endpoint based on consensus recommendations and practicality.[5,6] More recent research has demonstrated significant intraindividual variation in ALP, questioning the usefulness of ALP as a biomarker and/or primary endpoint in PSC.[15] The choice of ALP change as the sole primary endpoint may also have affected the results.

In conclusion, in this pilot trial, the novel DHODH inhibitor VC led to a significant improvement in ALP while demonstrating an excellent safety profile. These data support efforts to complete a randomized clinical trial with a larger patient cohort to determine the clinical relevance and significance of these findings.

REFERENCES

1. Hirschfield GM, Karlsen TH, Lindor KD, Adams DH. Primary sclerosing cholangitis. Lancet. 2013;382:1587–99.
2. Gochanour E, Jayasekera C, Kowdley K. Primary sclerosing cholangitis: epidemiology, genetics, diagnosis, and current management. Clin Liver Dis (Hoboken). 2020;15:125–8.
3. Lindor KD, Kowdley KV, Harrison ME; American College of Gastroenterology. ACG clinical guideline: Primary Sclerosing Cholangitis. Am J Gastroenterol. 2015;110:646–59.
4. Williamson KD, Chapman RW. Primary sclerosing cholangitis: a clinical update. Br Med Bull. 2015;114:53–64.
5. Ponsioen CY, Chapman RW, Chazouillères O, Hirschfield GM, Karlsen TH, Lohse AW, et al. Surrogate endpoints for clinical trials in primary sclerosing cholangitis: review and results from an international PSC study group consensus process. Hepatology. 2016;63:1357–67.
6. Ponsioen CY, Lindor KD, Mehta R, Dimick-Santos L. Design and endpoints for clinical trials in primary sclerosing cholangitis. Hepatology. 2018;68:1174–88.
7. Hilscher M, Enders FB, Carey EJ, Lindor KD, Tabibian JH. Alkaline phosphatase normalization is a biomarker of improved survival in primary sclerosing cholangitis. Ann Hepatol. 2016;15:246–53.
8. Zhang H, Bernuzzi F, Lleo A, Ma X, Invernizzi P. Therapeutic potential of IL-17-mediated signaling pathway in autoimmune liver diseases. Mediators Inflamm. 2015;2015:436450.
9. Katt J, Schwinge D, Schoknecht T, Quaas A, Sobottka I, Burandt E, et al. Increased T helper type 17 response to pathogen stimulation in patients with primary sclerosing cholangitis. Hepatology. 2013;58:1084–93.
10. Herrlinger KR, Diculescu M, Fellermann K, Hartmann H, Howaldt S, Nikolov R, et al. Efficacy, safety and tolerability of

vidofludimus in patients with inflammatory bowel disease: the ENTRANCE study. J Crohns Colitis. 2013;7:636–43.
11. Muehler A, Kohlhof H, Groeppel M, Vitt D. Safety, tolerability and pharmacokinetics of vidofludimus calcium (IMU-838) after single and multiple ascending oral doses in healthy male subjects. Eur J Drug Metab Pharmacokinet. 2020;45:557–73.
12. Muehler A, Kohlhof H, Groeppel M, Vitt D. The selective oral immunomodulator vidofludimus in patients with active rheumatoid arthritis: safety results from the COMPONENT study. Drugs R D. 2019;19:351–66.
13. Muehler A, Peelen E, Kohlhof H, Gröppel M, Vitt D. Vidofludimus calcium, a next generation DHODH inhibitor for the treatment of relapsing-remitting multiple sclerosis. Mult Scler Relat Disord. 2020;43:102129.
14. Hahn F, Wangen C, Häge S, Peter AS, Dobler G, Hurst B, et al. IMU-838, a developmental DHODH inhibitor in phase II for autoimmune disease, shows anti-SARS-CoV-2 and broad-spectrum antiviral efficacy in vitro. Viruses. 2020;12:1394.
15. Trivedi PJ, Muir AJ, Levy C, Bowlus CL, Manns MP, Lu X, et al. Inter- and Intra-individual variation, and limited prognostic utility, of serum alkaline phosphatase in a trial of patients with primary sclerosing cholangitis. Clin Gastroenterol Hepatol. 2021;19:1248–57.

How to cite this article: Carey EJ, Eaton J, Clayton M, Gossard A, Iqbal S, Ullah H, et al. A pilot study of vidofludimus calcium for treatment of primary sclerosing cholangitis. Hepatol Commun. 2022;6:1589–1597. https://doi.org/10.1002/hep4.1926